

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: **A61M 29/00**
 (11) International Publication Number: **WO 98/34669**
 (43) International Publication Date: **13 August 1998 (13.08.98)**

(21) International Application Number: **PCT/US98/02222**
 (22) International Filing Date: **9 February 1998 (09.02.98)**
 (30) Priority Data: **US/797,743** **7 February 1997 (07.02.97)** **US**
 (71) Applicant: **ENSOVASC LTD., INC. (US/US);** Suite 108, 15001 Walden Road, Montgomery, TX 77356 (US).
 (72) Inventors: **SUMMERS, David, P.;** 3158 Canterbury Lane, Montgomery, TX 77356 (US). **SEE, Jackie, R.;** 2519 Emerald Avenue, Las Vegas, NV 89120 (US).
 (74) Agent: **NICHOLS, Nick, A., Jr.;** Nick A. Nichols Jr., P.C., P.O. Box 16399, Sugar Land, TX 77496-6399 (US).

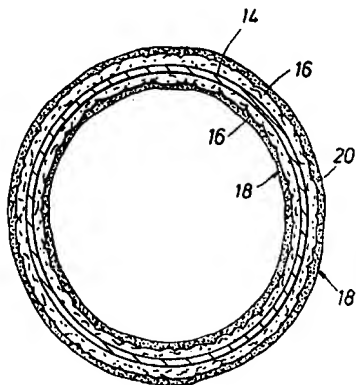
Published

With international search report.

(54) Title: **COMPOSITION AND METHOD FOR MAKING A BIODEGRADABLE DRUG DELIVERY STENT**

(57) Abstract

A stent or vascular graft (10) for supporting a blood vessel or organ lumen is coated with a biodegradable, resorbable and hemocompatible surface substrate (16). Biologically active microspheres (20) which controllably release the biologically active agent into the vessel wall or organ (12) to inhibit restenosis of the stent (10) is embedded in the stent substrate (16). The biologically active microspheres (20) include encapsulated PGE1 in a water soluble polyethylene glycol mix (18), which over a period of time dissolves and releases the PGE1 into the vessel wall or organ (12).



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GB	United Kingdom	LV	Latvia	SE	Sweden
AZ	Azerbaijan	GR	Greece	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GW	Guinea-Bissau	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MM	Myanmar	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IN	India	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NZ	New Zealand	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	PL	Poland	VM	Viet Nam
CG	Congo	KE	Kenya	PT	Portugal	VU	Vanuatu
CH	Switzerland	KG	Kyrgyzstan	RO	Romania	ZW	Zimbabwe
CI	Cote d'Ivoire	KP	Democratic People's Republic of Korea	RU	Russian Federation		
CN	China	LA	Laos	SD	Sudan		
CU	Cuba	LB	Lebanon	SE	Sweden		
CZ	Czech Republic	LC	St. Lucia	SG	Singapore		
DE	Germany	LI	Liechtenstein				
DK	Denmark	LK	Sri Lanka				
EE	Estonia	LR	Liberia				

COMPOSITION AND METHOD FOR MAKING A BIODEGRADABLE DRUG DELIVERY STENT

BACKGROUND OF THE INVENTION

The present invention relates to biodegradable drug delivery stents, particularly stents coated with a biocompatible substance impregnated with antithrombocyte/antithrombin agents released over a period of time to reduce or eliminate restenosis in the blood vessel.

Percutaneous endovascular stenting was conceived in the late 1970's as a way to prevent both acute occlusion and late restenosis after catheter intervention, but initial clinical results of coronary stenting in 1987 were plagued by high (>20%) acute and subacute thrombosis and were restricted to use as "bailout" for threatened or acute vessel closure. In recent years, stent outcomes have improved progressively with better placement techniques and in 1995, an estimated 700,000 stents were implanted world-wide. Recent STRESS (Stent Restenosis Study, 1994) and BENESTENT trials (Belgium-Netherlands Stent, 1995) demonstrated that stenting of native coronary arteries is associated with greater procedural success. The trials demonstrated that fewer acute, adverse events and less angiographic restenosis and lower rates of 8-months target vessel revascularization occurred than in conventional balloon angioplasty. Stents are now used as primary treatment and secondary bailout.

Despite their utility, stents have been plagued by two problems, namely, acute occlusion due to thrombosis and persistent occurrence of restenosis. Recent studies show that coronary stenting results in significant platelet, polymorphonuclear leukocyte, and macrophage activation, as well as activation of the coagulation pathway which induce clots despite passivation and/or anti-coagulation treatment of the stent surface. This limitation relates to the surface exposure of adhesion receptors on activated platelets to the foreign surface of the stent, producing the aforementioned thrombogenic activity that must be countered with intense anti-coagulation regimens. Subacute stent thrombosis occurs most frequently during the first few days after implantation and almost always in the first two weeks. Thereafter, neointimal cells including proliferating smooth muscle cells from the vessel wall and endothelial hyperplastic cells encompass the stent surface and ameliate the risk of stent thrombosis.

Notwithstanding the above, vascular stents have proven to be of great therapeutic value in the treatment and prevention of complications relating to percutaneous transluminal coronary angioplasty (PTCA). Mechanical problems of the vessel wall, i.e., vessel dissection, the most

frequent cause of acute closure in about 25% of patients leading to acute myocardial infarction associated with PTCA, is virtually eliminated with stents. However, such major acute and chronic adverse events persist in more than 25% of patients. One of the most important causes is the thrombogenicity of the stent itself. Despite increased biocompatibility currently available, stents have less than hemocompatibility and are further limited because of late incidence in virtually all stents of restenosis, potentially fatal late complications from clotting and an aggressive type of in-stent restenosis resistant to therapy. In-stent restenosis is much more difficult to treat than PTCA restenosis, frequently resulting in coronary artery bypass grafting (CABG).

In addition to the morbidity and mortality, stents are more expensive than PTCA and require longer hospitalization in order to provide anticoagulant and antispasm therapy due to the induction of thrombogenicity and spasm by the stent, a foreign object, introduced into the vascular wall. The heavy anticoagulation required can produce major bleeding events and vascular complications, often necessitating surgical intervention.

What is desired is a stent coating of antithrombotic, antispasm agents which will biodegrade over time, eluting drugs into the vessel wall to inhibit these complications and obviating systemic oral or intravenous or intraarterial drug delivery with heightened cost and side effect profile. PGE1 is the ideal antithrombotic agent and antispasmodic agent, which also has antiproliferative effects on the smooth muscle cell (SMC). In addition, PGE1 is very effective in inhibiting platelet activation and deposition, and produces blocking effects on leukocyte adhesion molecules through the lipoxygenase and leukotriene pathway and blocks macrophage migration and aggregation at the injury site.

Much work has been done to both passivate and/or biologically enhance the surface properties of stents so as to reduce the need for anticoagulants and the like. For example, Bolz, et al., described a process for coating stents with a semi-conductor (Bolz, A., et al, Coating of Cardiovascular Stents with a Semi-Conductor to Improve Their Hemocompatibility, Tex. Heart Inst. Jour. 1996;23:162-6) which provided electrical passivation of the surface charge of stents thereby neutralizing the attraction of coagulating proteins. Other investigations have grafted both active and neutral substances to stents, such as hirudin or neutral collagen, in attempts to ameliorate coagulation. (Prielzel, K. et al. Inhibition of Neointimal Proliferation with a Novel Hirudin/Prostacyclin Analog Eluting Stent Coating in an Animal Overstretch Model, Abstract,

Circulation, Supplement 1, Vol. 94, No. 8, Oct. 15, 1996, p. 1-260); U.S. Patent No. 5,342,387, Summers, Artificial Support for a Blood Vessel. These coatings have proven less than successful in ameliorating the total problem. Two factors, cellular proliferation within the stent lumen itself and late vessel wall remodeling, remain unsolved.

Restenosis within and around the stent is a process of chronic new endothelial and medial cellular growth, and remodeling of the vessel after intervention which usually occurs by the third month postintervention. Restenosis is a continuum of extracellular matrix rebuilding after stretching, which continues from the time of PTCA, peaking at three months and unusually terminating after six months. Although percutaneous delivery of stents has been shown to slightly reduce the frequency of restenosis as compared to PTCA, when such lesions do occur within a stent, they have been considered to result from intimal proliferation with smooth muscle cells, the predominate cell type, and are resistant to treatment, since PTCA is generally precluded and rotational atherectomy or CABG usually required. Therefore, it is obvious that stent occlusion is a two-phase problem having an acute phase in which platelet, leukocyte, macrophage aggregation, and thrombosis is the primary concern and a chronic and late-phase problem in which intimal in-stent proliferation and vessel wall remodeling is the primary concern. It is, therefore, an object of the instant invention to overcome both acute and chronic concerns with the foregoing invention.

Since most cellular interactions are protein mediated, the prevention or reduction in protein adsorption to a stent would serve to prevent cellular attachment and subsequent events that may otherwise render the stent materials biocompatible but in doing so, produce the unwanted adverse effects of not coating the stent. A stent coated with a composition of both biocompatible agents and drug eluting systems such as PGEI to retard initial harmful vascular cellular and thrombosis mechanisms, while allowing normal subsequent acceptance of the stent by the vessel wall by orderly vascular cell covering with endothelial and medial cells, and compatible treatment for post-PTCA complications would be desirable.

Poly-L-lactic acid (PLLA)/Poly-caprolactone (PCL) blends of aliphatic polyester polymers have proven to be both biodegradable, resorbable and hemocompatible. Depending on the ratio of PLLA to PCL, these coatings can provide a benign substrate that provides a microporous structure that can efficiently be impregnated with biologically active microsphere such as liposomes in the range of 20nm to 1000nm.

It is therefore an object of the invention to provide a stent having a PLLA/PCL coating substrate formed thereon and impregnating the coating substrate with biologically active microspheres.

It is a further object of the invention to provide a stent coating whereby the coating substrate is coated with a layer of PGEI-encapsulated liposomes which release PGEI over an extended period of time.

SUMMARY OF THE INVENTION

The present invention provides a stent coated with a biodegradable, resorbable and hemocompatible surface substrate. The substrate is impregnated with biologically active microspheres which controllably release the biologically active agent into the vessel wall to inhibit restenosis of the stent. The biologically active microspheres include encapsulated PGEI in a water soluble polyethylene glycol mix, which over a period of time dissolves and releases the PGEI into the vessel wall.

BRIEF DESCRIPTION OF THE DRAWINGS

So that the manner in which the above recited features, advantages and objects of the present invention are attained can be understood in detail, a more particular description of the invention, briefly summarized above, may be had by reference to the embodiments thereof which are illustrated in the appended drawings.

It is noted, however, that the appended drawings illustrate only typical embodiments of this invention and are therefore not to be considered limiting of its scope, for the invention may admit to other equally effective embodiments.

Fig. 1 is an enlarged view of two loops of a double-helix stent according to the invention located within a blood vessel;

Fig. 2 is a sectional view of the stent of the invention depicting the substrate coating formed on the surface of the stent;

Fig. 3 is a sectional view of the stent of the invention depicting the substrate coating and encapsulated biologically active microspheres formed on the surface of the stent; and

Fig. 4 is an enhanced microscopic view of the stent substrate coating of the invention.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

Referring first to Fig. 1, the coated stent of the invention, generally identified by the reference numeral 10, is shown located in a blood vessel 12. The stent 10 is shown as having a double-helix wire configuration positioned in a blood vessel for illustrative purposes. It is understood that the stent 10 may comprise other configurations and be positioned in any organ requiring support to open a lumen or passageway without departing from the scope of the present invention. Referring still to Fig. 1, the stent 10 is located in the vessel 12 in the region where the vessel wall has collapsed and requires support to maintain the vessel 12 in an open condition. While it has been shown that stents have great therapeutic value, stents have suffered from unacceptable hemocompatibility which typically results in restenosis of the vessel 12 which is much more difficult to treat.

Referring now to Fig. 2, stent 10 of the invention comprises a wire 14 which, as noted above, is configured in the shape of a double-helix. The wire 14 is coated with a substrate 16. The substrate 16 encapsulates the stent wire 14 and comprises, in the preferred embodiment, a 50:50 combination of PLLA/PCL which is swollen in 40% trifluoroacetic acid with polyethylene oxide (PEO) to first open the pores of the substrate 16 for loading of microspheres or liposomes in microspherical geometries (according to Rajasubramanian, et al, Fabrication of Resorbable Microporous Intravascular Stents For Gene Therapy Applications, ASAIO Journal, 1994, M584-89). The acidic combination etches the skin surface and the pore walls of the substrate 16, rendering the polymer surfaces more hydrophilic. The etched pores 17 of the substrate 16 have an irregular pore surface and define a mean pore size of 150-200 nm long axis and 50-75 nm short axis. The porosity of the substrate 16 is in the range of 19% to 44%.

After swelling, the surface of the substrate 16 is coated with a slurry of PGEI-encapsulated liposomes in a polyethylene glycol (PEG) mix 18 having a neutral pH which first fills and then collapses the pores 17 of the substrate 16 about the embedded liposomes 20, as best shown in Fig. 4. The pores 17 are filled with liposomes 20 of 100 nm to 200 nm diameters, providing a mean average of about 1000 liposomal microspheres per pore. What remains then is a modified surface coating, producing biocompatible, cell-non-adhesive surface of PEG and lyophilized liposomal microspheres. PEG itself has been shown to have protein-repelling activity when immobilizing on a surface due to its hydrophilicity, chain mobility, and lack of ionic charge. Since PEG is water-soluble, platelet adhesion and thrombus formation is further limited

by a continuous semi-dissolved molecular disassociation which actually increases the hydrophilicity of the stent substrate 16, making surface adhesion on the stent 10 even more difficult.

After placement of the stent 10 in the vessel 12, the water-soluble surface polymers of PEG begin to dissolve thereby exposing the surface embedded liposomes 20. The liposomes 20 are exposed in stages; the first exposure being those on or close to the surface coating of the substrate 16. The liposomes 20 embedded within the pores 17 of the substrate 16 remain inactivated until both the PEG overlay mixture 18 and the portion of PLLA/PCL encompassing the closed pores 17 of the substrate 16 has been resorbed and thereby releasing the liposomes 20, a process that may continue over a period of time up to six months.

Once the outer coating of the substrate 16 is "dissolved" and upon activation, the liposomes 20 release their biologically active agent by leaking out the liposomes 20 into the vessel wall 12. In the preferred embodiment of the present invention, the active agent encapsulated within the liposomes 20 is prostaglandin E1 (PGE1), a natural-occurring fatty acid of the cyclopentenone family.

The release of the liposomal PGE1 produces a secondary effect that is both synergistic and antagonistic. It is synergistic with the PEG, in that the PEG tends to accumulate at the injured tissue and with long chain lengths further inhibits cellular interactions at the polymer surface, but in addition, the timed release of PEG1 produces powerful chronic antagonistic chemotaxis to thromboxane and leukotriene actions on the platelets and injured vessel wall while modulating the proliferation of smooth muscle cells (SMC) and extracellular matrix within the media of the blood vessel 12. This two-stage process continues to produce inhibition of protein absorption and hence cellular interactions at the biomaterial surface while releasing powerful inhibitions of platelet aggregation and modulators of cell growth in the region of the vessel wall 12 where the stent 10 is located. The protein inhibiting action of the biologically active agent continues over a predetermined period of weeks or months or until endothelialization of the biosurface is complete. Of particular note, the labile PEG end-groups on these modified surfaces can be made to serve as attachment sites for suitable biospecific peptides that result in a surface that could potentially adhere to only one particular cell type, such as endothelial cells in the case of stents or vascular grafts.

While a preferred embodiment of the invention has been shown and described, other and

further embodiments of the invention may be devised without departing from the basic scope thereof, and the scope thereof is determined by the claims which follow.

CLAIMS:

1. A stent for supporting a blood vessel, said stent having a hemocompatible substrate formed thereon, and further including a substrate coating embedded with biologically active microspheres.
- 5 2. The stent of claim 1 wherein said substrate includes one or more layers of a resorbable PLLA/PLC combination, said combination providing a biologically compatible, structurally sufficient porous substrate surface for bonding with said substrate coating.
3. The stent of claim 2 wherein said substrate coating comprises a water soluble polymer mixture such as polyethylene glycol, polyethylene oxide, polyvinylpyrrolidone,
- 10 polyethylene oxazoline and other such water soluble polymers, said substrate coating including encapsulated liposomes.
4. The stent of claim 1 wherein said substrate comprises Poly-L-lactic acid/Polycaprolactone and Polyethylene glycol/lipophilized prostaglandin E1 mixture, said prostaglandin being encapsulated in liposomal microspheres in a size range of 20nm to
- 15 1000nm.
5. The stent of claim 2 wherein said substrate coating is water soluble and resorbable, producing a continuous and gradual release of liposomal prostaglandin embedded in said substrate coating.
6. The stent of claim 1 wherein said substrate includes irregular surface pores capable of
- 20 containing releaseable microspheres, said microspheres being liposomal prostaglandin E1.
7. The stent of claim 6 wherein said pores are in the order of 105nm to 200nm long axis and 50nm to 75nm short axis.
8. The stent of claim 7 wherein said pores retain and release said microspheres at a
- 25 predetermined rate.
9. The stent of claim 1 wherein said substrate has a porosity of 18% to 45%.
10. A method of modifying cellular response in a blood vessel or organ to a disease, injury or foreign body, comprising the steps of:
 - a) forming a hemocompatible substrate on a stent;
 - 30 b) embedding biologically active microspheres in a water soluble surface coating;
 - c) applying said surface coating on said stent substrate;

- d) positioning said stent in the blood vessel or organ; and
 e) controllably releasing said microspheres into the blood vessel wall or target organ.
11. The method of claim 10 including the step of swelling the substrate in 40% trifluoacetic acid with polyethylene oxide to open the pores of the substrate for loading the pores with liposomal microspheres.
12. A vascular graft for supporting a lumen, said graft having a hemocompatible substrate formed thereon, and further including biologically active microspheres embedded in a substrate coating.
13. The vascular graft of claim 12 wherein said substrate coating is water soluble and resorbable, producing a continuous and gradual release of liposomal prostaglandin embedded in said substrate coating.
14. The vascular graft of claim 13 wherein said substrate coating includes liposomes containing prostaglandin E1.
15. The vascular graft of claim 14 wherein said liposomes are in the size range of 20nm to 200nm.

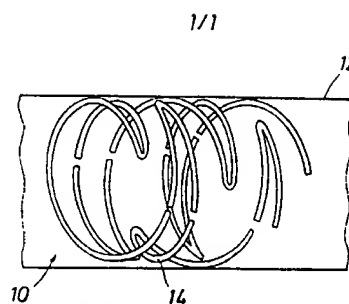


FIG. 1

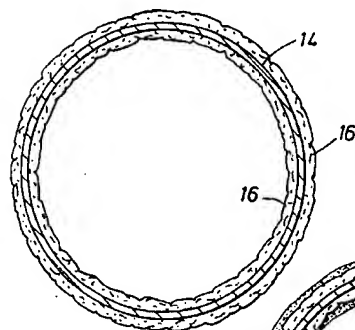


FIG. 2

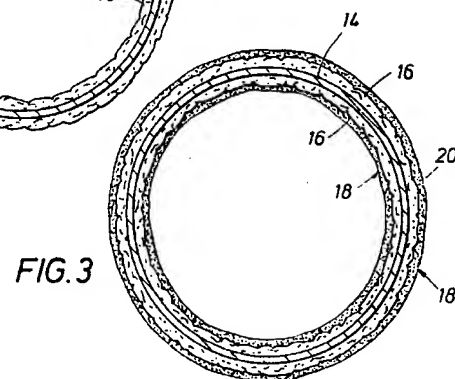


FIG. 3

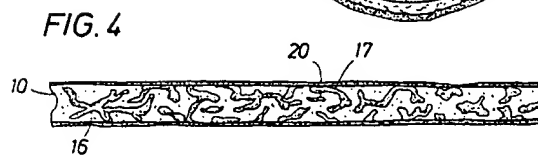


FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/02222

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61M 29/00

US CL : 606/194

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/450; 606/154, 194, 195, 198; 623/1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

Search Terms: stent, biocompatible, microsphere, resorbable

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of documents, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 5,674,242 A (PHAN et al) 07 October 1997, cols. 5-7, 15 and 16.	1, 3, 10
Y,P		2, 4-9
Y	US 5,464,450 A (BUSCEMI et al) 01 November 1995, col. 5, lines 11-37.	2, 4-9
Y	US 5,082,664 A (LENK et al) 21 January 1992, whole document.	4-9
A,P	US 5,624,411 A (TUCH) 29 April 1997, whole document.	1-15
A,P	US 5,697,967 A (DINH et al) 16 December 1997, whole document.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* "I" prior documents published after the international filing date or priority date and not in conflict with the applicant but cited to understand the principles or theory underlying the invention
"A" documents defining the general state of the art which is not considered to be of particular relevance	"X" documents of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B" earlier documents published on or after the international filing date	"Y" documents of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is considered with one or more other such documents, each contribution being relevant to a portion disclosed in the art
"L" documents which may throw doubts on priority claim(s) or which is used to establish the publication date of another document or other special reason (as specified)	"G" documents of the same parent family
"O" documents referring to an oral disclosure, use, exhibition or other means	
"P" documents published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

20 APRIL 1998

Date of mailing of the international search report

11 MAY 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized official

JULIAN W. WOO

Telephone No. (703) 308-0421

Form PCT/ISA/210 (second sheet)(July 1992)*